JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 13, 2024
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PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Enhanced Decongestive Therapy in Patients With Acute Heart Failure

JACC Review Topic of the Week

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ABSTRACT

Because signs of congestion are associated with adverse outcomes in patients with acute heart failure (AHF), attempts were made to decongest patients as much as possible with diuretic agents (loop diuretic agents, thiazides, acetazolamide) or mechanical devices. Those interventions improved signs of congestion but failed to meaningfully improve patients' symptoms, improve quality of life, or reduce early readmissions or deaths. Recent studies have shown that implementation of guideline-directed medical therapies after an AHF admission led to both more decongestion and improved symptoms, quality of life, and outcomes. Therefore, for most patients with AHF whose symptoms and congestion can be controlled with loop diuretic agents, the main focus should be rapid guideline-directed medical therapy uptitration. Enhanced decongestion, ie, adding a second-line diuretic agent to a loop diuretic agent, should be reserved for those patients who do not respond to loop diuretic agents. (J Am Coll Cardiol 2024;83:1243–1252) © 2024 by the American College of Cardiology Foundation.

Congestion has been recognized as the most common sign of heart failure (HF) for centuries.[1] Over the last decades, it has been well established that congestion is associated with the main symptoms of acute heart failure (AHF)—led by dyspnea and with adverse outcomes such as recurrent HF admissions and death.[2]

A universally accepted diagnostic tool for quantification of congestion is lacking. Many definitions were suggested; however, some modifications on the score suggested in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) study[2]—including measures such as dyspnea, fatigue, orthopnea, jugular venous pulse (JVP), rales, and pedal edema/ascites assessed on a standardized scale—have been used in many studies and were the basis of most of the studies reported in the following text. In those studies, attempts were made to decongest patients (as measured by the same set of signs) with the hope that if signs of congestion are reduced (such as peripheral edema), patients' symptoms and outcomes will follow given the previously mentioned association between signs of congestion and patients' symptoms and short-term adverse outcomes.

EARLY STUDIES OF ENHANCED DECONGESTION

Early studies of enhanced decongestion are shown in Figure 1. Congestion is the landmark feature of AHF, and clinical severity is determined by the complex interplay among precipitants, the underlying cardiovascular (CV) substrate, and the patient's noncardiac comorbidities (Figure 2). Given that congestion is

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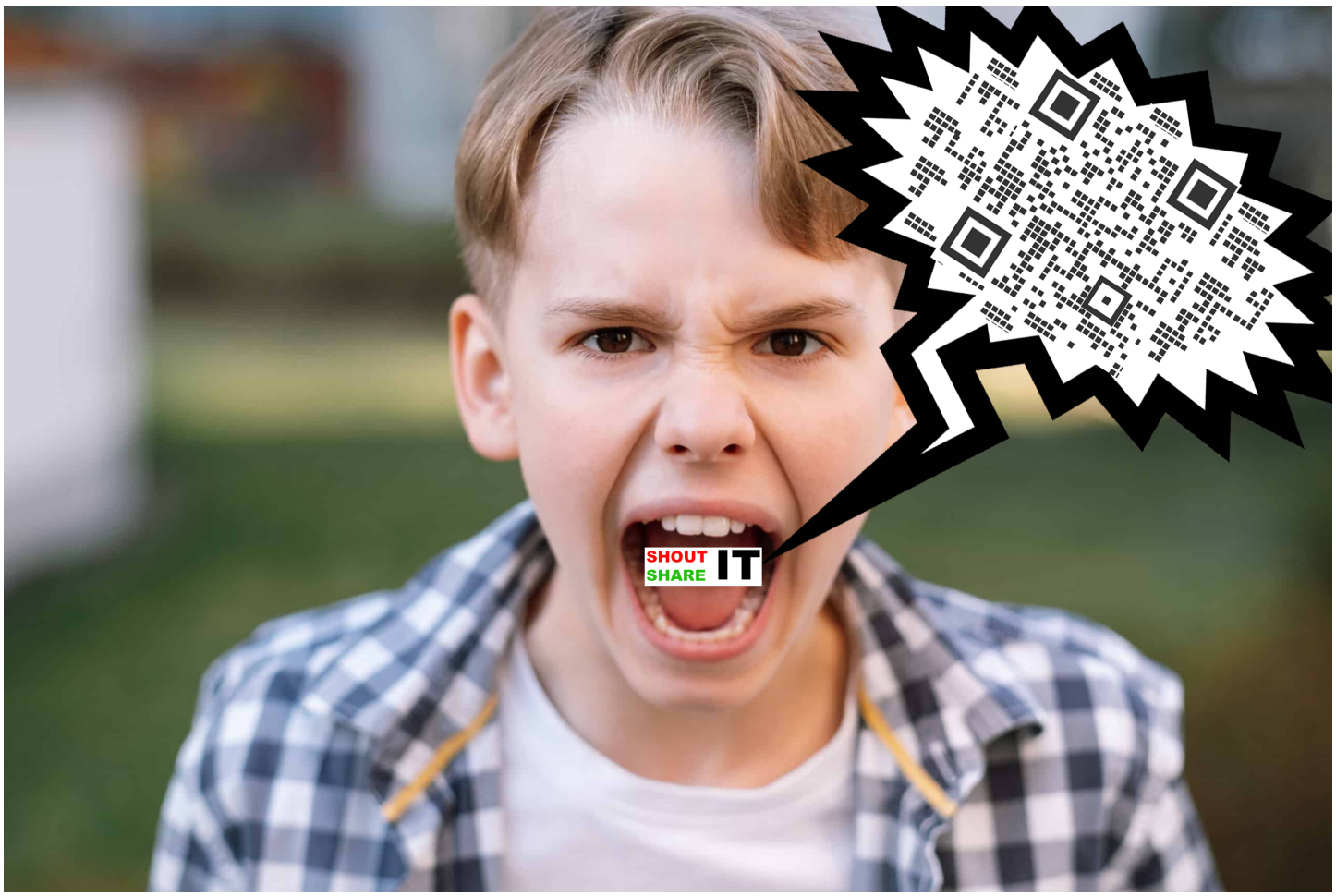
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 4, 2023; revised manuscript received January 18, 2024, accepted January 18, 2024.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2024.01.029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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

eGFR = estimated glomerular filtration rate

GDMT = guideline-directed medical therapy

MRA = mineralocorticoid receptor antagonist

SGLT2 = sodium-glucose cotransporter 2

such a pivotal sign of HF and its strong association with both symptoms and adverse outcomes, enhanced decongestion—ie, adding a second-line diuretic agent or device to loop diuretic agents—was proposed as an important treatment target in AHF. However, multiple studies, small and large, that examined many kinds of medications and devices have failed to show that decongestion can make patients admitted for AHF either significantly feel better or live longer—defining features of a beneficial intervention (**Central Illustration**). Initially, in small phase 2 studies, adding higher doses of loop diuretic agents, adenosine antagonists, aquaretic agents, and ultrafiltration to usual doses of loop diuretic agents showed encouraging results in reducing weight and sometimes even improving signs of congestion. However, the phase 3 studies that followed, in which these agents were tested on top of a background therapy with loop diuretic agents, were largely disappointing. For instance, the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study[3] showed a small improvement in dyspnea in patients assigned rolofylline, but also showed more worsening renal function and no effect on 60-day outcomes compared with placebo. Similar results were observed in a study comparing higher vs lower doses of loop diuretic agents[4] with a trend toward improved patient symptoms but also a trend toward a greater increase in creatinine. In the EVEREST study,[5] the aquaretic drug tolvaptan had significant beneficial effects on patients' weight and a small effect on dyspnea as well as on most symptoms and signs of congestion. Importantly, no differences compared with placebo were observed with respect to adverse events or significant changes in kidney function, electrolytes, or blood pressure. However, no differences were observed with respect to longer-term outcomes such as all-cause death, CV death, or HF readmissions. In a National Institutes of Health-sponsored study, ultrafiltration was found to be inferior to a pharmacologic therapy control with respect to a bivariate endpoint of weight and creatinine changes at 96 hours, primarily caused by an increase in creatinine in the ultrafiltration arm.[6] There was also a higher proportion of serious adverse events through 60 days with ultrafiltration and a numerically, although nonstatistically significant, higher risk of 60-day all-cause death and death or hospitalization in the ultrafiltration arm.

HIGHLIGHTS

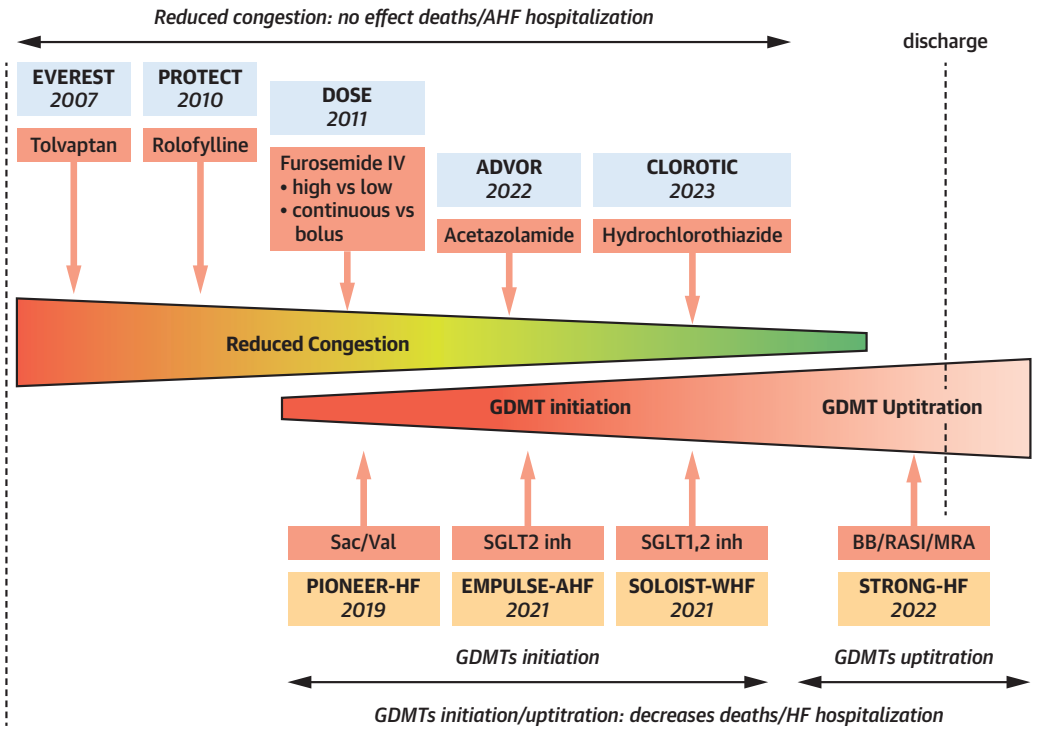
- Congestion in patients with AHF is associated with poor outcomes and frequent hospital readmissions.
- Enhanced decongestion leads to minimal improvement in symptoms or outcomes in patients with AHF.
- Greater focus on GDMT after discharge can improve outcomes for patients hospitalized with AHF.

These pivotal studies together with many smaller ones suggest that enhanced decongestion therapy combining loop diuretic agents with a second diuretic agent or device is effective in decongestion; ie, in most cases, it induces more weight loss and some improvement in signs of congestion. However, results with respect to patient symptoms and clinical outcomes were disappointing. The effects on patients' symptoms, when statistically significant such as those observed in PROTECT and EVEREST,[3,5] were small and largely of questionable clinical significance, only reaching statistical significance because of the large size of the studies. On the other hand, these beneficial effects were accompanied by trends toward, and sometimes even statistically significant, deleterious effects on renal function and reductions in blood pressure and potassium. Effects on clinical outcomes such as readmissions and deaths have never been demonstrated. Some of this lack of effect may relate to the natural course of AHF patients treated with loop diuretic agents. Results of trials in all-comers with AHF suggest that most patients admitted for AHF are treated with small doses of intravenous (IV) and then oral loop diuretic agents, and their symptoms and signs of congestion largely resolve within 2 days of admission;[7] by day 7 or discharge, 80% of patients have no to very minimal symptoms and signs of congestion.[2] These data combined with the neutral results of all enhanced decongestion studies lead most experts to consider that for the majority of AHF patients, further decongestion therapy beyond loop diuretic agents administered IV and then orally is not needed.

RECENT STUDIES OF ENHANCED DECONGESTION

In recent years the understanding of diuretic resistance and its importance in AHF has evolved, highlighting that in some patients with AHF, persistent congestion remains a significant problem that beyond its association with longer-term adverse outcomes

FIGURE 1 Randomized Clinical Trials of Decongestion and GDMT Uptitration

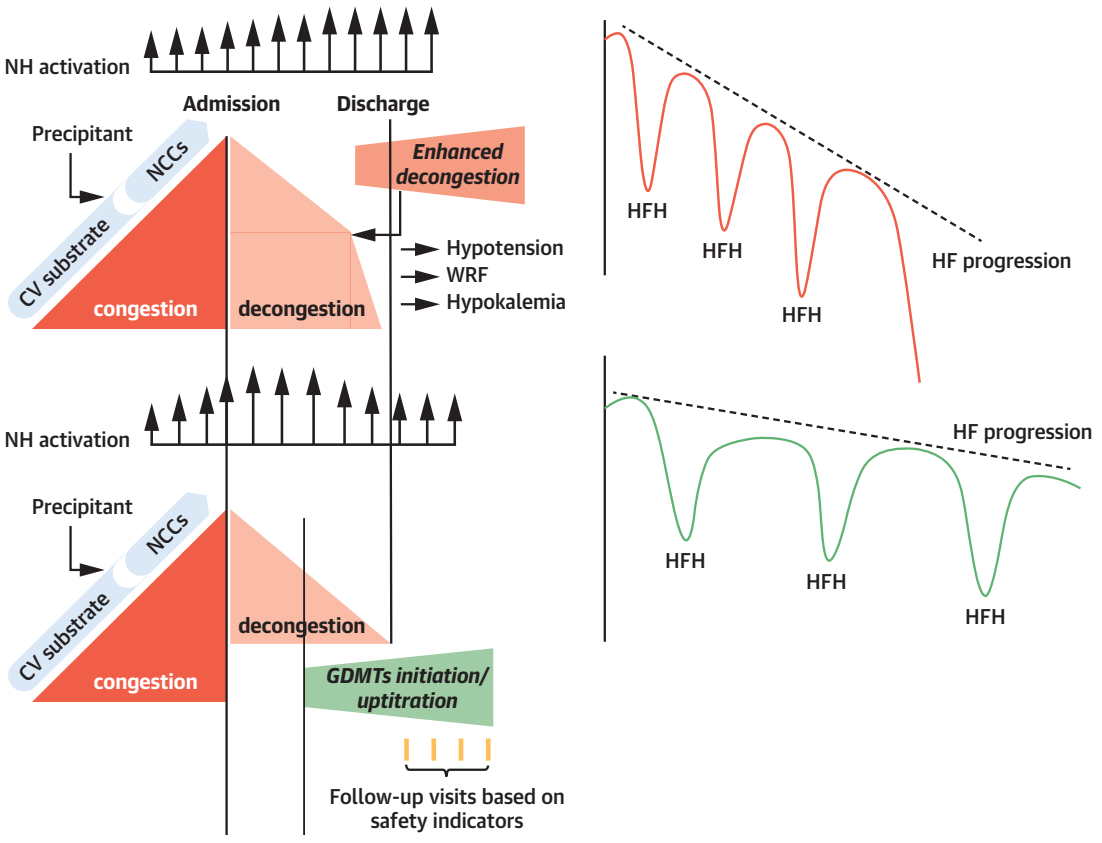


Presentation of randomized trials investigating enhanced decongestion strategies (EVEREST, PROTECT, DOSE, ADVOR, CLOROTIC) and randomized trials investigating early initiation (PIONEER-AHF, EMPULSE-AHF, SOLOIST-WHF) and uptitration (STRONG-HF) of guideline-directed medical therapies (GDMTs). Each trial is represented with study medication and year of publication. ADVOR = Acetazolamide in Acute Decompensated Heart Failure with Volume Overload; AHF = acute heart failure; BB = beta-blockers; CLOROTIC = Combining Loop With Thiazide Diuretic Agents for Decompensated Heart Failure; DOSE = Diuretic Optimization Strategies Evaluation; EMPULSE = EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; HF = heart failure; MRA = mineralocorticoid receptor antagonist; PIONEER-AHF = Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; PROTECT = Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; RASi = renin angiotensin system inhibitor; Sac/Val = sacubitril valsartan; SGLTi = sodium-glucose cotransporter inhibitor; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; STRONG-HF = Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP testinG, of Heart Failure therapies.

prolongs the admission.[8] This understanding coupled with the growing published reports supporting the use of spot sodium measurements as an important marker for inefficient diuresis[9] and hence, natriuresis as a marker to guide decongestive therapy, have led to the conduct of a new wave of studies examining enhanced decongestion therapies for patients with AHF (Figure 1). In PUSH-AHF (Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure), natriuresis-guided diuretic therapy in patients with AHF significantly improved natriuresis and diuresis up to 48 hours but without affecting all-cause mortality and/or HF hospitalization at 180 days.[10]

Two of these studies, investigating enhanced decongestion via additional natriuretic agents, were published in the last 2 years. The first, the ADVOR (Acetazolamide in Acute Decompensated Heart Failure with Volume Overload) study,[11] examined the administration of acetazolamide or placebo in 519 patients with AHF and signs of peripheral fluid overload and high natriuretic peptides. The study's primary endpoint was successful decongestion at 3 days, based on a congestion score comprising peripheral edema, pleural effusion, and ascites. The secondary endpoints included 90-day death or readmission for HF, length of stay (LOS), and changes in quality of life measured by the EuroQOL-5 Dimension Questionnaire (EQ-5D) at days 4 and 90. The study met its primary endpoint showing that both at day 4 and discharge more patients in the acetazolamide arm had successful decongestion

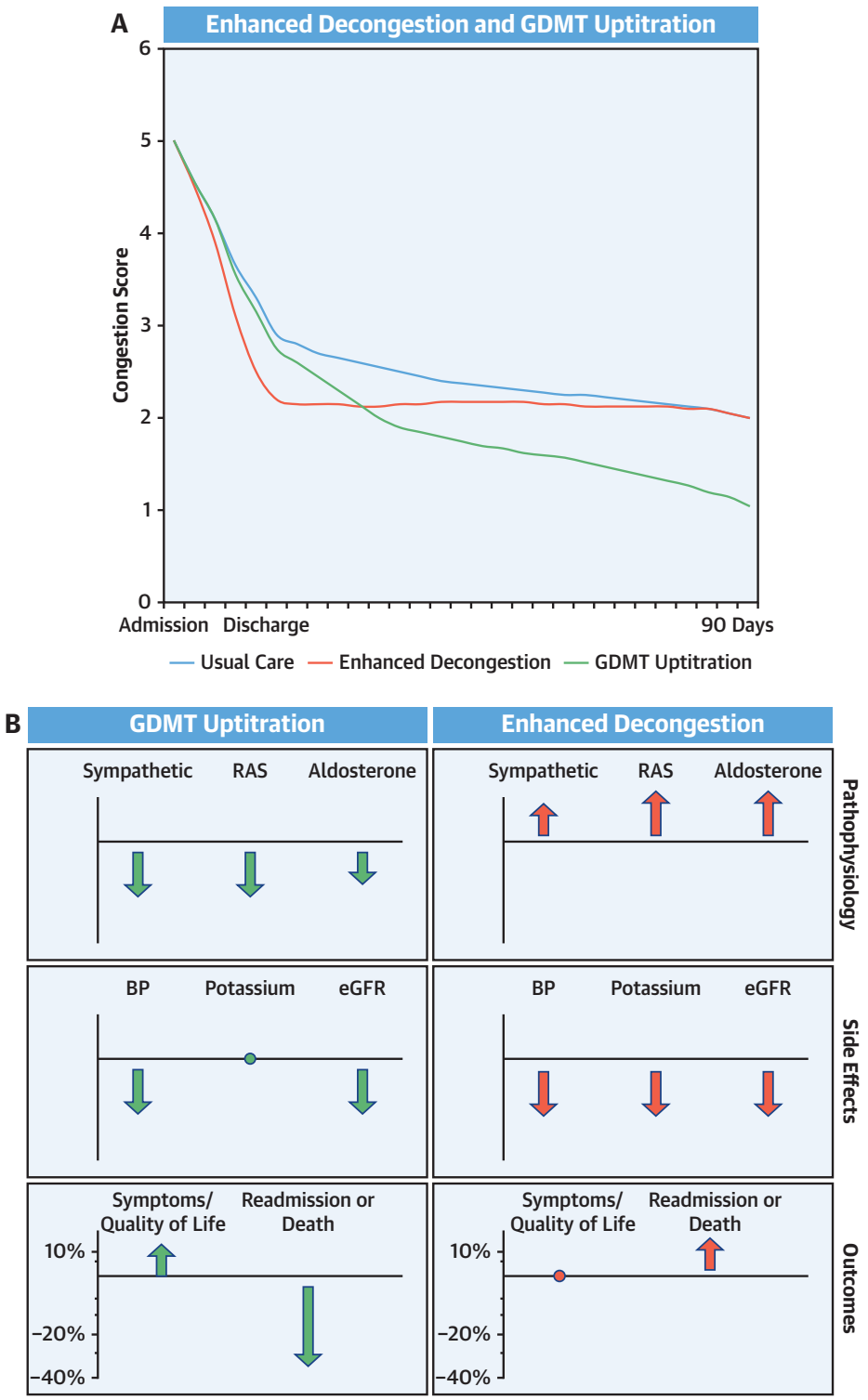
FIGURE 2 The Relationship Between Decongestion and Uptitration of GDMTs in AHF



Congestion is the landmark feature of acute heart failure (AHF), and clinical severity is determined by the complex interplay among precipitants, the underlying cardiovascular (CV) substrate, and the patient's noncardiac comorbidities (NCCs). Enhanced decongestion strategies (adding a second-line diuretic or device to intravenous loop diuretic agents), was proposed as an important treatment target in AHF, but all clinical trials have failed to show that decongestion has been associated with lower mortality and/or heart failure hospitalization (HFH), while leading to neurohormonal (NH) activation and significant side effects (electrolyte abnormalities, worsening renal function (WRF), and blood pressure decreases) that may delay and prevent guideline-directed medical therapy (GDMT) implementation. Opposite, early initiation of GDMTs, as well as intense uptitration, determines lower NH activity and decrease of long-term mortality and/or HFH.

than in placebo. This was associated with a nominally significant 1-day reduction in LOS. However, no differences were seen regarding changes in symptoms as measured by EQ-5D at day 4 (EQ-5D VAS improved numerically more in control with mean changes of 10.3 points vs 9.4 points), and 3-month risks of readmission for HF (18.4% vs 17.4%) and mortality (15.2% vs 12.0%) were numerically higher in the active group, although numbers were too small to draw firm conclusions. There was a trend to lower potassium in the acetazolamide arm during treatment ($P = 0.053$)[12] and more events of hypokalemia in the acetazolamide arm during the whole follow-up period (23.4% vs 14.7%, $P = 0.0134$).[11] During treatment, blood pressure was lower in the active group (P values were not reported and were estimated by us): at day 1 systolic blood pressure 115 ± 19 mm Hg in active vs 125 ± 22 mm Hg in placebo ($P \approx 0.001$), at day 3 systolic BP was 114 ± 19 mm Hg vs 120 ± 20 mm Hg ($P \approx 0.005$), P values estimated by us. Similar effects were observed with respect to renal function as assessed by estimated glomerular filtration rate (eGFR): at day 3 eGFR was 35 mL/min/1.73 m^2 (26-48 mL/min/1.73 m^2) in active vs 39 mL/min/1.73 m^2 (29-54 mL/min/1.73 m^2) ($P \approx 0.002$), P values estimated by us.[11] This was reflected also in acetazolamide being associated with a higher incidence of worsening renal function as defined by a rise in creatinine ≥0.3 mg/dL during the treatment period (40.5% vs 18.9%; $P < 0.001$), but there was no difference in creatinine after 3 months.[13] Of note, in the ADVOR study, despite patients being admitted for AHF with persistent congestion, only

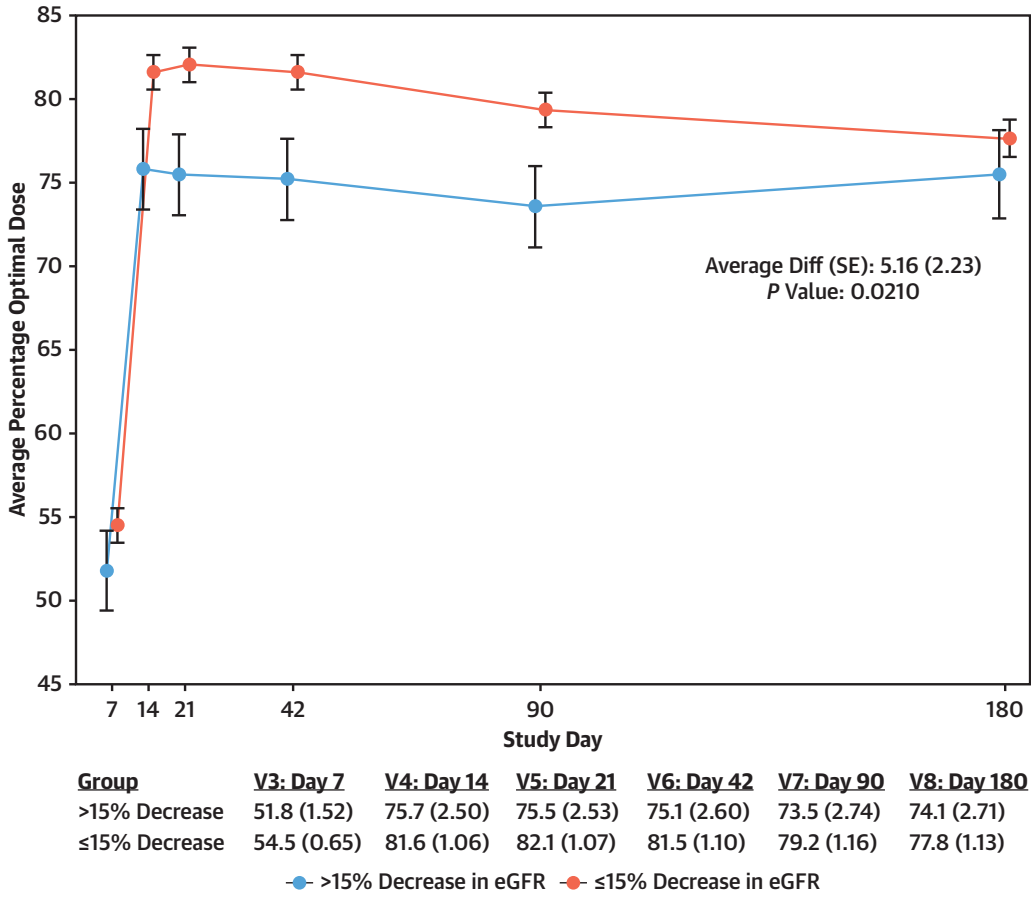
CENTRAL ILLUSTRATION **Comparison Between Enhanced Decongestion Strategies and Uptitration of Guideline-Directed Medical Therapies**



Cotter G, et al. J Am Coll Cardiol. 2024;83(13):1243-1252.

Although both strategies are associated to decongestion, uptitration of guideline-directed medical therapies (GDMTs) produces a decrease persistent decrease in congestion (A) without neurohormonal activation, leading to better quality of life and outcomes. Enhanced decongestion therapy only improves congestion in the short-term, leads to neurohormonal activation, and has no effect on quality of life and outcomes. BP = blood pressure; eGFR = estimated glomerular filtration rate; RAS = renin angiotensin system.

FIGURE 3 Percentage of Guideline-Directed Medical Therapy Dose After Early eGFR Decrease in Acute Heart Failure



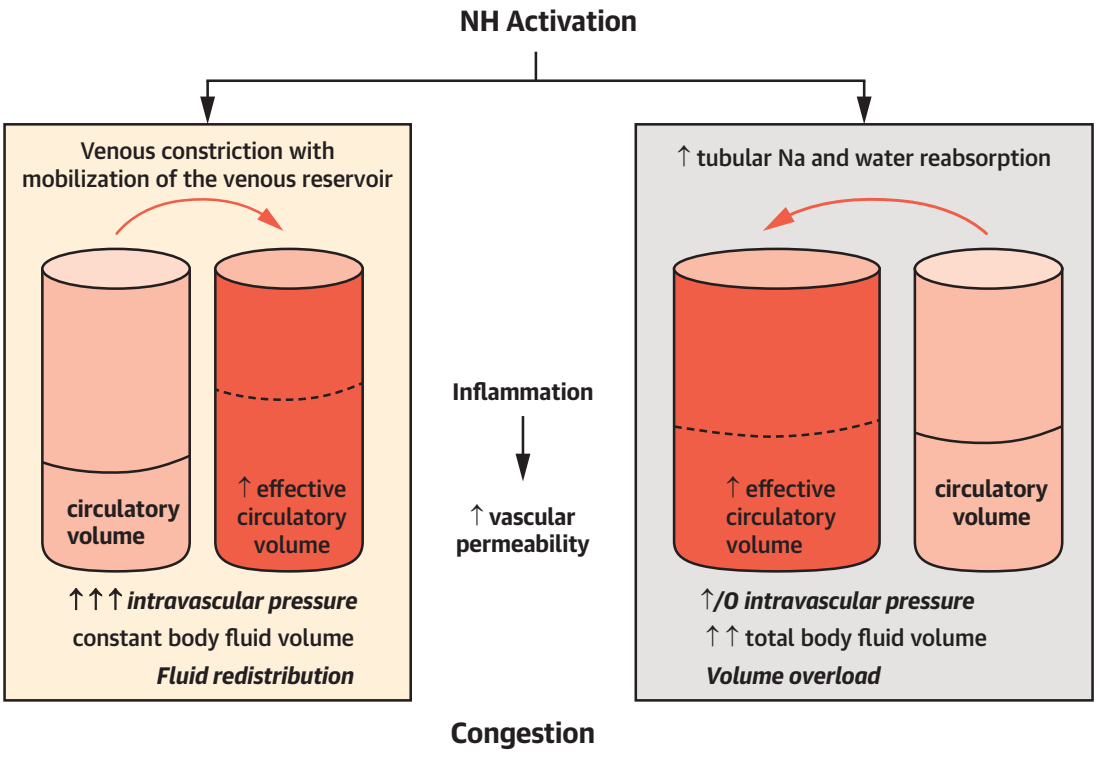
Group	V3: Day 7	V4: Day 14	V5: Day 21	V6: Day 42	V7: Day 90	V8: Day 180
>15% Decrease	51.8 (1.52)	75.7 (2.50)	75.5 (2.53)	75.1 (2.60)	73.5 (2.74)	74.1 (2.71)
≤15% Decrease	54.5 (0.65)	81.6 (1.06)	82.1 (1.07)	81.5 (1.10)	79.2 (1.16)	77.8 (1.13)

The trajectory of the average percentage of optimal dose during follow-up for a decrease in estimated glomerular filtration rate (eGFR) at week 1, showing significantly lower average of optimal doses of guideline-directed medical therapy during follow-up for patients with an early decrease in eGFR ($P = 0.021$).

about one-half of the patients were treated by a renin-angiotensin system inhibitor of any kind, with no change during admission, and only one-half received a mineralocorticoid receptor antagonist (MRA) during admission and two-thirds at discharge.

The second study was the CLOROTIC (Combining Loop With Thiazide Diuretic Agents for Decompensated Heart Failure) study,[14] which enrolled 230 patients with AHF and a history of dependence on furosemide 80 to 240 mg/d for at least 1 month. There was no requirement for congestion to be present at randomization. Patients were randomized to receive hydrochlorothiazide or placebo. The study's 2 coprimary endpoints were change in weight and dyspnea at 72 hours. There were multiple secondary endpoints further examining decongestion, symptoms, and readmission and death. The study's first primary endpoint was met showing a significant 0.8-kg higher weight loss in the active group. With regards to the second primary endpoint, there was a numerically larger improvement in dyspnea in active as measured by area under the curve representing the change in visual analog scale score over time: 960 vs 720 mm·h ($P = 0.497$). No significant benefit in favor of active was seen with respect to dyspnea area under the curve at 96 hours, or patient-rated dyspnea improvement at 72 hours or day 5. Rates of renal impairment and hypokalemia were increased, and similarly to ADVOR, 90-day risks of all-cause rehospitalizations (37.7% vs 34.5%) and death (20.2% vs 16.4%) were numerically higher in the active group. Of note, patients enrolled in CLOROTIC had mostly preserved ejection fraction (56%) and low eGFR (43.2 mL/min/1.73 m^2), suggesting that significant renal impairment may have been more prominent than HF in their congestion.

FIGURE 4 Pathophysiology of Congestion Congestion-Driven Pressures and Volume Expansion in AHF



Increased neurohormonal activation—common in patients with decompensated heart failure—may lead to a functional shift of blood from the splanchnic veins, increasing circulatory filling pressures despite constant total blood volume. This type of congestion is less responsive enhanced decongestion via natriuresis. Similarly, neurohormonal (NH) activation increases proximal tubular Na and water reabsorption resulting in overall fluid overload, and this type of congestion is responsive to natriuresis-based strategies.

The results of ADVOR and CLOROTIC are largely similar. In both studies, an enhanced decongestion therapy was tested combining loop diuretic agents with a second-line diuretic. Both studies showed that this approach successfully decongests patients. However, the studies showed little improvement in patients' symptoms and outcomes with this approach. In CLOROTIC, dyspnea improvement numerically favored active treatment, but there was no change in LOS, and in ADVOR there was numerically less symptom improvement in the active group, but LOS was reduced with a nominally significant *P* value. Both studies were associated with more adverse events in the active group, such as hypokalemia and fall in eGFR. In ADVOR, blood pressure decreased more in the active group. A meta-analysis we performed combining the 2 studies estimated risks of 90-day mortality of 13.3% in control vs 16.6% in patients treated by enhanced decongestion therapy (HR: 1.26; 95% CI: 0.89-1.77; $P = 0.19$). Because decreases in blood pressure, eGFR, and potassium have all been shown in retrospective analysis to be associated with increased mortality in AHF,[15-17] the trend toward increased mortality observed in COLORIC and ADVOR cannot be dismissed as a chance finding. It is possible that an adequately sized study might find an increased mortality risk with enhanced decongestion.

ENHANCED DECONGESTION VS GUIDELINE-DIRECTED MEDICAL THERAPY UPTITRATION DURING AN AHF EVENT

What should we conclude from the results of CLOROTIC and ADVOR, and should these studies change the way we treat patients with AHF? The answer to the first question is that CLOROTIC and ADVOR have largely confirmed previous studies conducted 10 to 20 years ago, suggesting that enhanced decongestion therapy in AHF has a small effect on patients' symptoms and/or LOS but is not associated with better outcomes. Although a direct comparison is obviously

not possible, the results of ADVOR and CLOROTIC seem to be less promising than those of EVEREST because in both ADVOR and CLOROTIC, the number of patients enrolled were small; side effects with regards to changes in blood pressure, creatinine, and potassium were clinically meaningful; and there were worrying trends toward increased mortality. In contrast, EVEREST showed a symptom improvement, albeit small, that was not associated with more adverse events. To the second question of whether these studies should change clinical practice the answer is probably no. As previously stated, most patients admitted with AHF have very significant improvement in dyspnea and no signs of congestion within 48 hours from admission when treated with small doses of loop diuretic agents. For these patients, additional decongestion therapy is not needed and the focus of treatment after the initial stabilization should be rapid uptitration of guideline-directed medical therapy (GDMT) (**Figure 2**). This was suggested by us >20 years ago[18] and has been confirmed by recent AHF studies[19] such as STRONG-HF (Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies),[20] EMPULSE (EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd),[21] SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure),[22] PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode),[23] and PARAGLIDE (Prospective comparison of ARNI with ARB Given following stabiLization In DEcompensated HFpEF)[24] (**Figure 1**). In this regard, unnecessary enhanced decongestion therapy, via induction of electrolyte abnormalities, creatinine increases, and blood pressure decreases, may delay and prejudice GDMT implementation (**Figure 1**).[25] An example of such delay in GDMT uptitration can be seen in the STRONG-HF study.[25] In this study, a worsening of kidney function as measured by a decrease in eGFR of >15% was associated with a trend toward less GDMT uptitration especially during the first crucial weeks after the AHF event (**Figure 3**).

Therefore, we believe that in the majority of patients in whom decongestion can be achieved effectively with combined oral and IV loop diuretic agents, enhanced decongestion may lead to substantial side effects and delay GDMT uptitration without improving patients' symptoms or preventing adverse outcomes. In the minority of patients in whom simple decongestion with IV and oral loop diuretic agents fails, additional decongestion therapies should be considered. However, it is possible that the simplest way to improve congestion in patients unresponsive to loop diuretic agents is early initiation of MRA, ARNI, and sodium-glucose cotransporter 2 inhibitors (SGLT2i), which are known to both improve short- and long-term decongestion as well as improve outcomes. The exact sequence of therapies in patients with diuretic (**Central Illustration**) resistance or residual congestion in AHF is hard to determine and more studies are needed. A recent study comparing an SGLT2i with metolazone was not conclusive[26] showing trends toward less decongestion but also fewer metabolic abnormalities in patients treated with dapagliflozin.

An interesting question is why was LOS reduced in ADVOR if patients' symptoms were not improved? This intriguing finding suggests that the physician's decision on patient discharge may have been driven by signs of congestion more than by patients' symptoms and despite patients remaining significantly undertreated by GDMT. Maybe one lesson should be that we need to refocus our assessments of the patients' "dischargeability" more on patients' symptoms and achieving as high a GDMT dose as possible predischarge then on assessing signs of congestion.

An important unanswered dilemma is why, despite congestion being associated with both more symptoms and more adverse outcomes, its relief by enhanced decongestion therapies does not make patients feel better or live longer. The answer to this question is not clear. Given the fact that all enhanced decongestion therapy studies had minimal to no effects on symptoms and did not affect longer-term outcomes, we should consider whether congestion is a marker of disease severity in HF and not its main driver. The pathophysiology of congestion is multifactorial as a result of the dynamic relationship among cardiac function, the roles of interstitial and intravascular fluid compartments, the vascular permeability, oncotic pressure, and how the kidney manages the sodium and water at renal level.[27] There is a disconnection between congestion-driven pressures and congestion-driven volume expansion, resulting in different clinical presentations with different response to decongestion strategies (**Figure 4**). Data from registries demonstrated that pulmonary congestion is more common than systemic congestion (74% vs 56%), and very often these 2 pathophysiologies coexist.[28] Also, many studies have shown that fluid accumulation in the way of weight gain is not universally seen in patients before an AHF admission, undermining the concept that solely fluid accumulation (via increased Na and water renal reabsorption) drives congestion in AHF and,

therefore, enhanced decongestion may not resolve the core cause of AHF.[29] Some studies have suggested that congestion, especially lung congestion, is more related to changes in water clearance through endothelial basement membranes that are caused by inflammatory activation.[30] We have long known that inflammatory activation occurs commonly in AHF—could it be that it is the driver of congestion and not simple fluid overload?

However, the blockage of the neurohormonal adrenergic system has been shown to improve CV function[31-38] and at the same time improve diuresis and diuretic efficiency.[39-44] Therefore, the main pathway to improving long-term congestion in patients with HF is to counteract the core mechanisms that lead to cardiac dysfunction and reduce the diuretic efficiency in the kidneys; once these mechanisms are corrected, the improvement in diuresis from their combined effects is likely to lead to substantial decongestions as has been seen in STRONG-HF[20] and EMPULSE.[21] Enhancing diuresis while not improving these underlying mechanisms, on the other hand, leads to short-term improved congestion but may lead to increased neurohormonal activation and worsening the core processes of HF rather than improving them,[45] explaining potentially the increased side effects and numerical worst outcomes after such enhanced diuretic treatment.

CONCLUSIONS

Recent studies examining enhanced decongestion strategies in patients with AHF have largely confirmed studies conducted 10 to 20 years ago. These studies suggest that enhanced decongestion does not substantially make patients feel better; is associated with side effects with regards to electrolytes, creatinine increases, and blood pressure decreases; and is in some cases associated with trends towards more adverse post-discharge outcomes. We believe that enhanced decongestion should therefore be reserved for patients who cannot be decongested by loop diuretic agents and where enhanced GDMT therapy with MRAs, ARNi and SGLT2s is not possible or has been exhausted.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Cotter and Davison are employees of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics; and are directors of the Heart Initiative, a nonprofit organization. Dr Chioncel has received grants from Servier.

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REFERENCES

1. Hajar R. Congestive heart failure: a history. *Heart Views*. 2019;20:129.

2. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J*. 2013;34:835–843.

3. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med*. 2010;363:1419–1428.

4. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797–805.

5. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007;297:1332–1343.

6. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304.

7. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2013;381:29–39.

8. Ter Maaten JM, Valente MAE, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. *Nat Rev Cardiol*. 2015;12:184–192.

9. Biegus J, Zymliński R, Fudim M, et al. Spot urine sodium in acute heart failure: differences in prognostic value on admission and discharge. *ESC Heart Fail*. 2021;8:2597–2602.

10. ter Maaten JM, Beldhuis IE, van der Meer P, et al. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med*. 2023;29:2625–2632.

11. Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N Engl J Med*. 2022;387:1185–1195.

12. Dhont S, Martens P, Meekers E, et al. Sodium and potassium changes during decongestion with acetazolamide-A pre-specified analysis from the ADVOR trial. *Eur J Heart Fail*. 2023;25(8):1310–1319.

13. Meekers E, Dauw J, Martens P, et al. Renal function and decongestion with acetazolamide in acute decompensated heart failure: the ADVOR trial. *Eur Heart J*. 2023;44(37):3672–3682.

14. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44:411–421.

15. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, Van Veldhuisen DJ. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail*. 2009;11:847–854.

16. Matsue Y, Sama IE, Postmus D, et al. Association of early blood pressure decrease and renal function with prognosis in acute heart failure. *J Am Coll Cardiol HF*. 2021;9:890–903.

17. Caravaca Perez P, González-Juanatey JR, Nuche J, et al. Serum potassium dynamics during acute heart failure hospitalization. *Clin Res Cardiol*. 2022;111:368–379.

18. Cotter G, Moshkovitz Y, Milovanov O, et al. Acute heart failure: a novel approach to its pathogenesis and treatment. *Eur J Heart Fail*. 2002;4:227–234.

19. Cotter G, Davison B, Cohen-Solal A, Freund Y, Mebazaa A. Targeting the "vulnerable" period - first 3-6 months after an acute heart failure

admission - the light gets brighter. *Eur J Heart Fail*. 2023;25:30–34.

20. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400:1938–1952.

21. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28:568–574.

22. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128.

23. Morrow DA, Velazquez EJ, Devore AD, et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF Trial. *Circulation*. 2019;139:2285–2288.

24. Mentz RJ, Ward JH, Hernandez AF, et al. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. *J Am Coll Cardiol*. 2023;82:1–12.

25. ter Maaten JM, Mebazaa A, Davison B, et al. Early changes in renal function during rapid up-titration of guideline-directed medical therapy following an admission for acute heart failure. *Eur J Heart Fail*. 2023;25(12):2230–2242. https://doi.org/10.1002/EJHF.3074

26. Yeoh SE, Osmanska J, Petrie MC, et al. Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. *Eur Heart J*. 2023;44:2966–2977.

27. Núñez J, de la Espriella R, Rossignol P, et al. Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur J Heart Fail*. 2022;24:1751–1766.

28. Chioncel O, Mebazaa A, Harjola VP, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1242–1254.

29. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure—re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail*. 2008;10:165–169.

30. Chioncel O, Collins SP, Ambrosy AP, Gheorghiade M, Filippatos G. Pulmonary oedema-therapeutic targets. *Card Fail Rev*. 2015;1:38.

31. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263–e421.

32. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309(8):781–791.

33. Kosmala W, Rojek A, Przewlocka-Kosmala M, Wright L, Mysiak A, Marwick TH. Effect of aldosterone antagonism on exercise tolerance in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2016;68(17):1823–1834.

34. Bristow MR, Gilbert EM, Abraham WT, et al. for the MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation*. 1996;94(11):2807–2816.

35. Colucci WS, Kolias TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. *Circulation*. 2007;116(1):49–56.

36. Wong M, Staszewsky L, Latini R, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. *J Am Coll Cardiol*. 2002;40(5):970–975.

37. Sakai T, Miura S. Effects of sodium-glucose cotransporter 2 inhibitor on vascular endothelial and diastolic function in heart failure with preserved ejection fraction - novel prospective cohort study. *Circ Rep*. 2019;1(7):286–295. https://doi.org/10.1253/circrep.CR-19-0018

38. Nathaniel S, McGinty S, Witman MAH, et al. Impact of angiotensin receptor-neprilysin inhibition on vascular function in heart failure with reduced ejection fraction: a pilot study. *Physiol Rep*. 2022;10(5):e15209. https://doi.org/10.14814/phy2.15209

39. Hornych A, Safar M, Simon A, et al. Effects of captopril on prostaglandin and natriuresis in patients with essential hypertension. *Am J Cardiol*. 1982;49:1524–1526.

40. Chatur S, Claggett BL, Vardeny O, et al. Sacubitril/valsartan and loop diuretic requirement in heart failure with preserved ejection fraction in the PARAGON-HF trial. *Eur J Heart Fail*. 2023;25:87–94.

41. Bauersachs J, Fraccarollo D, Ertl G, et al. Striking increase of natriuresis by low-dose spironolactone in congestive heart failure only in combination with ACE inhibition: mechanistic evidence to support RALES. *Circulation*. 2000;102:2325–2328.

42. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142:1040–1054.

43. Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. *Eur J Heart Fail*. 2019;21:337–341.

44. Biegus J, Voors AA, Collins SP, et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J*. 2023;44:41–50.

45. Burnier M, Brunner HR. Neurohormonal consequences of diuretics in different cardiovascular syndromes. *Eur Heart J*. 1992;13(Suppl G):28–33.

KEY WORDS acute heart failure, enhanced decongestion, guideline-directed medical therapy